Hypocellular Philadelphia chromosome-positive mixed-phenotype acute leukemia successfully treated with dasatinib: A case report

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Abstract. Both hypocellular leukemia and Philadelphia (Ph) chromosome-positive mixed-phenotype acute leukemia (MPAL) are rare subtypes of leukemia showing unfavorable outcomes and lacking established optimal management. Ph-positive leukemia most often presents with hypercellularity and hypoplasia is a rare condition. The present study reports an extremely rare case of hypocellular biclonal Ph-positive MPAL, which was diagnosed by biopsy and genetic analysis of bone marrow, and successfully treated with dasatinib and steroids. Briefly, a 77-year-old man presented with pancytopenia and flow cytometry of bone marrow could not be evaluated due to hypocellularity. The patient was finally diagnosed with hypocellular Ph-positive MPAL by genetic analysis and immunostaining of bone marrow biopsy. Although blood cells recovered with methylprednisolone pulse administration alone for concurrent optic neuritis, hematopoietic function rapidly normalized with dasatinib administered after definitive diagnosis of Ph-positive leukemia. Dasatinib and oral prednisolone were continued following methylprednisolone pulse administration and the patient achieved molecular complete remission (CR) on day 140 of treatment; molecular CR was maintained thereafter without any severe adverse events. In conclusion, the combination of dasatinib and a steroid may be one of the tolerable treatment options for elderly patients with hypocellular biclonal Ph-positive MPAL. Furthermore, genetic analysis and immunostaining of bone marrow biopsy can help with the diagnosis of leukemia with hypocellular bone marrow.

Introduction

Mixed phenotype acute leukemia (MPAL) is a heterogeneous and rare subtype of acute leukemia (1-3). MPAL is characterized by immunophenotypic features of a multi-cell lineage, and is divided into biphenotypic and biclonal types. Approximately 25% of MPAL cases have a Philadelphia chromosome (Ph) (4,5). MPAL commonly diagnosed by the demonstration of leukemic cells expressing markers of more than one hematopoietic lineage (3). Ph-positive MPAL is more common among elderly populations, has higher white blood cell (WBC) counts at diagnosis, and resulting a worse prognosis than Ph-negative MPAL (4-7). Treatment according to the management of Ph-positive acute lymphoid leukemia (ALL) has usually been provided, but the optimal course of treatment for Ph-positive MPAL has not yet been established (8).

Hypocellular acute leukemia is another rare variant of acute leukemia that occurs more frequently among the elderly and shows a poor prognosis (9). Various regimens have been provided for hypocellular acute leukemia, but consensus remains lacking regarding the optimal treatment (10). To the best of our knowledge, no reports have addressed hypocellular MPAL despite Ph-positive and its treatment.

We report herein the case of an elderly man with hypocellular Ph-positive biclonal-type MPAL diagnosed by immunostaining of bone marrow biopsy and genetic analysis not flow cytometry because of hypocellularity of bone marrow. Dasatinib and prednisolone were useful for achieving long-term molecular remission without compromising the quality of life.

Case report

A 77-year-old Japanese man was admitted to our hospital with malaise and sudden loss of vision in the right eye. He had been treated for hypertension for the past 25 years, but had no history of hematological abnormalities. Eastern Cooperative Oncology Group performance status was 0. Physical examination revealed conjunctival pallor, grade II/VI ejection systolic murmur in the left parasternal area in the second to fourth intercostal space, and petechiae on bilateral upper and lower extremities. Clinical laboratory data showed: white blood cell count (WBC), $3.4x10^9$/l (neutrophils 71.0%, blasts 5.0%); hemoglobin, 7.6 g/dl; platelet count, $35x10^9$/l; serum ferritin level, 1,359 ng/ml; serum total protein, 6.1 g/dl; albumin, 3.8 g/dl; aspartate aminotransferase, 34 IU/l; and alanine aminotransferase, 53 IU/l. However, no other abnormalities were identified, including lactate dehydrogenase level, renal function, and markers of disseminated intravascular coagulation. Right optic neuritis

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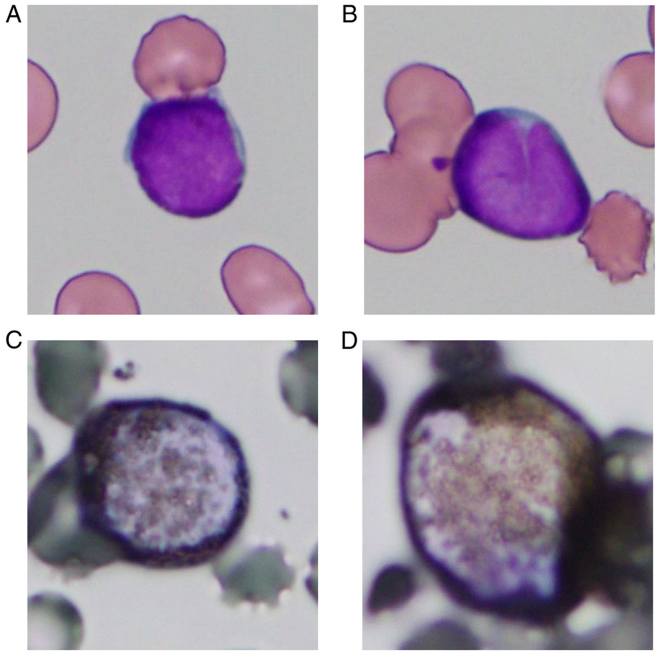

Figure 1. Blast cells in bone marrow. Bone marrow aspiration revealed hypocellular bone marrow. Blast cells on the bone marrow aspirate smear are shown. (A and B) May-Grunwald-Giemsa stain (magnification, x1,000). (C and D) Myeloperoxidase stain (magnification, x1,000).

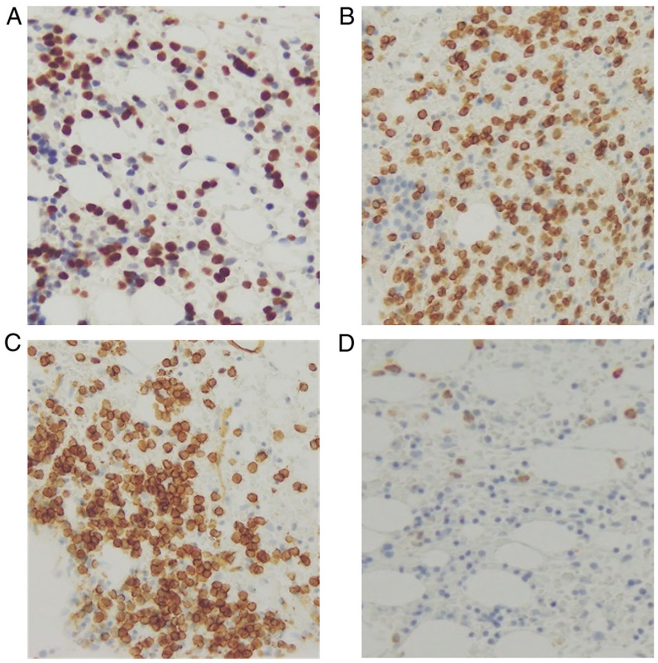

Figure 2. Immunohistochemical features of the bone marrow biopsy sample (magnification, x200). Low cellularity (20%) and proliferation of small round cells with poor nucleoli are observed in bone marrow. These small round abnormal cells are positive for (A) terminal deoxynucleotidyl transferase, (B) CD79a and (C) CD34, and negative for (D) myeloperoxidase immunostaining.

was diagnosed and intravenous methylprednisolone pulse therapy (1,000 mg/body/day, for 3 days) was immediately started. After methylprednisolone pulse therapy, oral prednisolone was continued at 25 mg/day.

He was referred to us for pancytopenia. Bone marrow aspirate smears showed a very low concentration of cells (nucleated cell count, $1.0x10^4/\mu l$), myeloid/erythroid ratio, 0.5; and 28% blasts among non-erythroid cells. Myeloperoxidase staining of blasts yielded positive results on cytochemistry (Fig. 1). The results of flow cytometry were unevaluable due to an insufficient number of blood cells available for measurement. The level of minor BCR-ABL mRNA in bone marrow was 10,000 copies/μg RNA. G-banding analysis of bone marrow revealed a 46,XY karyotype. Bone marrow biopsy revealed extremely low cellularity (20%) and proliferation of small round cells with poor nucleoli that were positive for terminal deoxynucleotidyl transferase (TdT), CD79a, and CD34, and negative for myeloperoxidase immunostaining (Fig. 2). The simultaneous presence of two different leukemic clones was demonstrated, and hypocellular Ph-positive biclonal MPAL was finally diagnosed.

Before the definitive diagnosis of leukemia, he was administered a second course of methylprednisolone pulse therapy for optic neuritis, followed by tapering of oral prednisolone to 10 mg/day. Bone marrow examination revealed peripheral blood cells had already recovered. Twenty-eight days after admission and initial administration of steroid, dasatinib at 140 mg/day and oral prednisolone at 30 mg/day were started as induction therapy. After initiating induction therapy with dasatinib, peripheral blood cell count immediately recovered significantly and normalized (Fig. 3). The patient was discharged 10 days after starting induction therapy and was continuously treated with dasatinib and oral prednisolone on an outpatient basis. The minor BCR-ABL fusion transcript in the bone marrow had disappeared according to real-time quantitative polymerase chain reaction at 140 days after starting induction therapy. Dasatinib was continued at 140 mg/day and oral prednisolone was tapered to 5 mg/day (Fig. 4). After achieving molecular complete remission (CR), he underwent 4 times of intrathecal chemotherapy (methotrexate 15 mg, cytarabine 40 mg, and prednisolone 10 mg) for central nervous system (CNS) prophylaxis. As of the time of writing, molecular CR has been maintained for 15 months with no serious adverse events and no loss in quality of life.

Discussion

While hypocellular leukemia has been rarely reported (9,11), there have been no reports of hypocellular leukemia with Ph-positive MPAL as in this case. It may suggest that bone marrow aspiration in a patient of hypocellular leukemia does not collect a sufficient number of cells, so the cell origin is not sufficiently evaluated, and even if it is Ph-positive MPAL, it is not properly diagnosed and underestimated. This case suggests that hypocellular leukemia found to be minor-BCR/ABL-positive MPAL may be expected to achieve long-term survival by combination therapy with TKI and steroids, thus supporting the usefulness of genetic analysis and immunostaining of bone marrow biopsy in hypocellular leukemia.

MPAL is a rare leukemic entity that accounts for 1.6-2.8% of adult acute leukemias (1,2), and is characterized by worse prognosis than single-lineage acute leukemia. In particular, the presence of the Ph chromosome adversely influences the prognosis of patients with MPAL (6,12-14). Although no

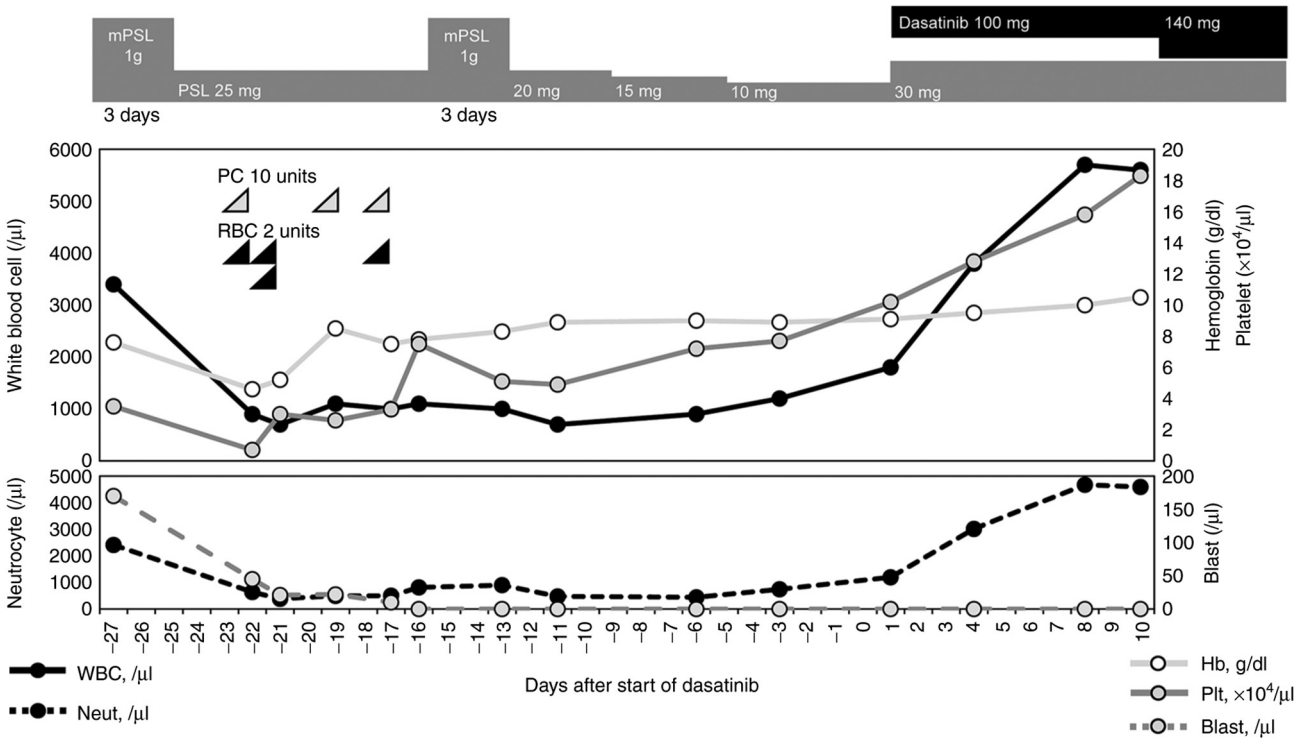

Figure 3. Clinical course during hospitalization of the present patient. Hb, hemoglobin; mPSL, methylprednisolone; Neut, neutrophils; PC, platelet transfusion; Plt, platelets; PSL, prednisolone; RBC, red blood cell transfusion; WBC, white blood cells.

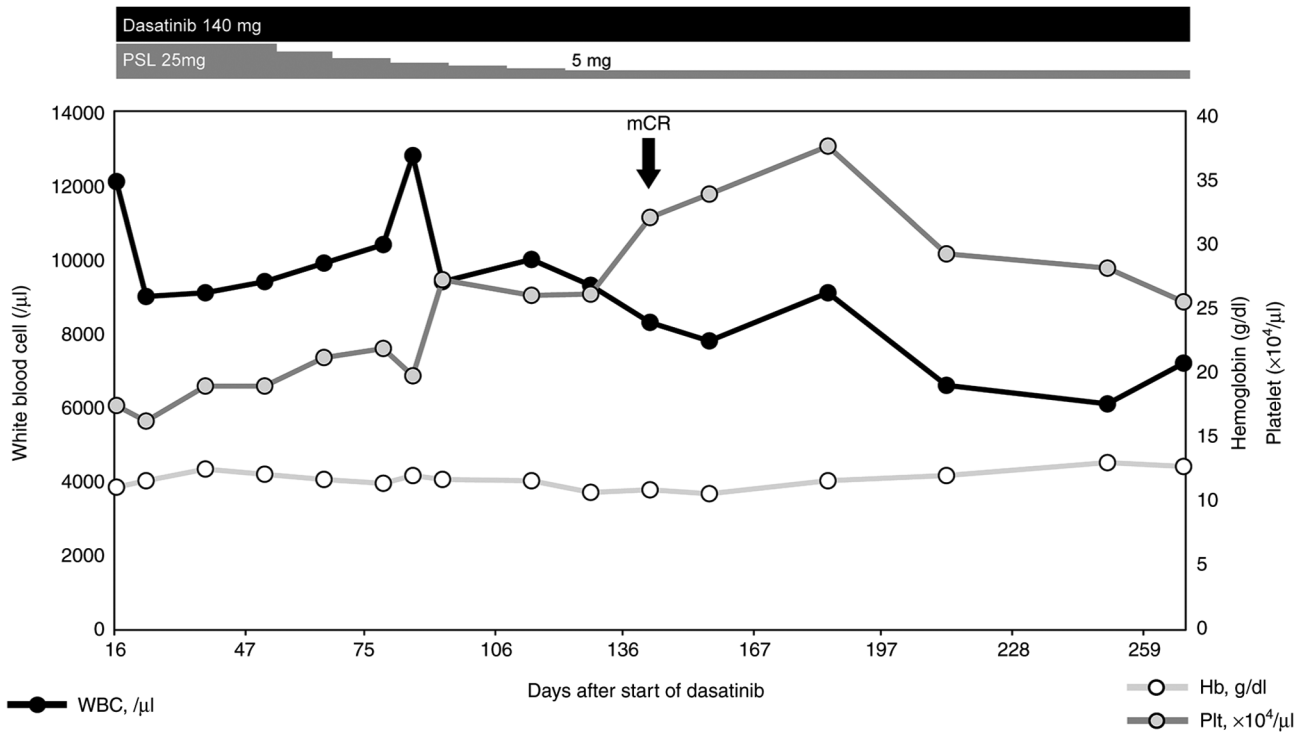

Figure 4. Clinical course of the present patient after discharge. Hb, hemoglobin; mCR, molecular complete remission; Neut, neutrophils; Plt, platelets; PSL, prednisolone; WBC, white blood cells.

consensus has been reached regarding treatment strategies for Ph-positive MPAL, certain cases have been managed similar to Ph-positive ALL in the recent tyrosine kinase inhibitor (TKI) era, with dramatically improved outcomes (7,8). Several reports have described TKI plus prednisolone or low-intensity chemotherapy as highly effective against elderly Ph-positive MPAL (15,16). There have been several cases of optic neuritis as the symptom of CNS involvement by acute leukemia (17-20). Steroids have been reported to relieve optic neuritis in ALL (18). Dasatinib has also been reported to cross

the blood-brain barrier and have an effect on the optic nerve infiltration of Ph-positive ALL (17,21). The cause of the optic neuritis of the present case has not been pathologically proven, but the possibility of leukemic involvement could not be denied. Dasatinib combined with prednisolone might be effective, and the leukemic cells in the CSF may have disappeared at the time of intrathecal chemotherapy after confirmation of hematological CR. The four times of intrathecal chemotherapy also seemed to contribute to the prevention of CNS relapse and maintenance of molecular CR.

Ph-positive leukemias generally present with high WBC counts because the gene products constantly activate intracellular signal transduction pathways via markedly increased tyrosine kinase activity (22). Despite expression of the Ph chromosome, the patient in our case presented with pancytopenia and hypocellular bone marrow. Ph-positive myelodysplastic syndrome has been reported (23,24), but WBC increased after expression of the Ph chromosome in these cases (23), and no reports have described hypocellular bone marrow despite the presence of the Ph chromosome. The optimal management for hypocellular leukemia has not yet been established. The case of an elderly woman with successful control using low-dose granulocyte colony-stimulating factor and oral prednisolone has been reported (25). In our case, gradual recovery of hematopoietic function after steroid alone and rapid normalization of hematopoietic function after addition of dasatinib were observed. Early administration of steroid might have contributed to the improved hematopoietic function. In addition, since the Ph chromosome also inhibits the proliferation of normal blood cells (22), suppression of Ph-positive clones by dasatinib may have restored normal hematopoiesis.

We have reported an unusual case of hypocellular biclonal MPAL despite the Ph expression. Even in cases of hypocellular leukemia, physicians should keep in mind of the Ph-chromosome expression. Genetic analysis and immunostaining of bone marrow biopsy can aid the correct diagnosis of the origin of leukemia blasts when it is unanalyzable by flow cytometry due to the hypocellular bone marrow. The clinical course of our patient demonstrated the efficacy and tolerability of dasatinib combined with steroid therapy for elderly patients with hypocellular Ph-positive MPAL.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SL contributed to the conception and the design of the study, the literature review and manuscript writing, data interpretation and manuscript revision. KF and YK contributed to data interpretation, manuscript discussion, and figure creation. HW, TH and HT helped with the design of the study, data interpretation, manuscript discussion and manuscript revision, and approved of the final manuscript version to be published. SL and KF confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for publication.

Competing interests

The authors declare that they have no competing interests.

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